Grocott staining showed irregularly branched hyaline septate hyphae and conidia. The organisms isolated from the fungal ball were identified as *Paecilomyces* species.

In contrast to the patient described by Chow et al. [6], neither of our patients cleared the pulmonary fungus ball after several months of therapy with voriconazole, despite the in vitro susceptibility of the fungal isolates. We administered voriconazole at the standard dosage of 200 mg po b.i.d. At this dosage, the expected steady-state serum levels with normal 90% absorption are 2.1–4.8 mg/mL [9], concentrations that are well above the voriconazole MIC for the fungal strains isolated from the patients. The failure of voriconazole treatment might have been due to low penetration of the drug beyond the outer layers of the fungus ball, resulting in insufficient intracavitary levels.

Although the lesions did not show a reduction in size, for one of our patients, results of sputum cultures became negative. The surrounding paracavitary shadowing on the CT scan for this patient suggested that chronic necrotizing pulmonary aspergillosis may have coexisted with the aspergilloma. The 2 entities are probably a continuum of the same pathological process [3], and it is believed that patients with chronic necrotizing pulmonary aspergillosis may actually respond to systemic antifungal therapy.

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References


CD4+ T Lymphocytes and Cryoglobulins in Patients Coinfected with HIV and Hepatitis C Virus: Forgetting the Hidden CD4+ Cell Subsets

SIR—Coinfection with HIV and hepatitis C virus (HCV), with its associated clinical features, represents one of the most important problems in the field of infectious diseases. Particularly in the past few years, some interesting findings on mixed cryoglobulins have been reported; nevertheless, some discrepancies exist about the pathogenesis of vasculitis in HIV-HCV coinfection [1–3]. An interesting article on the prevalence of mixed cryoglobulins in relation to the CD4 cell count in patients coinfected with HIV and HCV was recently published [4]. In this study, Aaron et al. [4] showed that there was a higher prevalence of cryoglobulins detected among the patients with a CD4+ cell count of ≥200 cells/μL, and, in light of their results, they concluded that cell-mediated immunity could contribute to mixed cryoglobulin pathogenesis in HIV-HCV coinfection. Even if these results are in contrast to those of other studies [2, 3], the study raises some important issues concerning the value of an exhaustive immune-system assessment in patients coinfected with HIV and HCV. With regard to these issues, we have the following questions.

How can Aaron et al. [4] attest to the role of cell-mediated immunity in cryoglobulin pathogenesis on the basis of the CD4+ cell count of ≥200 cells/μL? It is well known that CD4+ Th lymphocytes present different subsets with different competencies during an immune response [5]. In particular, 2 distinct subsets have been identified: CD4+ Th1 lymphocytes, which produce IFN-γ and IL-2, and are involved in cell-mediated immunity, and CD4+ Th2 lymphocytes, which secrete IL-4 and IL-10, and are implicated in humoral immunity through B cell stimulation [5–7]. Furthermore, it has been shown recently that the presence of cryoglobulins in HIV–HCV–coinfected patients was associated with a lower CD4+ cell count [3].

Thus, without determination of CD4+ cell subsets and the cytokines network by flow cytometry or ELISA, what evidence can corroborate the hypothesis of an influence of cell-mediated immunity on cryoglobulin production? A CD4+ T lymphocyte peripheral blood count should not be considered as just a marker of a single cell-compartment evaluation; rather, it should be considered as an expression of the whole of different subsets, both for immunocompromised and im-
munoreconstituted patients. In this context, it should be noted that even if the level of CD4+ T cells is globally reduced or increased, the percentage of one of the T cell subtypes could be increased or reduced with respect to the other subtypes, with an important influence on host defence, as suggested by Autran et al. [8] and other researchers [9, 10]. Indeed, with respect to the possible association between CD4+ cell count and the level of cryoglobulins and given the possible involvement of B cells, as Aaron et al. [4] report, it should seem logical that in patients with such vasculitis there would be an increased CD4+ humoral immunity response that stimulates B cells by means of the IL-4 and IL-10 network [6, 7], rather than a Th1 cell–mediated immune response.

In conclusion, we think that the evaluation of the CD4+ cell count alone gives us few elements to assess whether cell-mediated immunity or humoral immunity take part in the pathogenesis of cryoglobulinemia during HIV-HCV coinfection. A wider analysis of CD4+ T cell subsets, by use of simple and reliable 2-color flow cytometry, coupled with an evaluation of the role of HAART should be performed to gain a better understanding of these events and to determine future therapy.

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References


Reply to Perrella et al.

Sir—We thank Dr. Perrella and colleagues [1] for their interesting comments on our article [2] that showed that patients coinfected with HIV and hepatitis C virus (HCV) who have a CD4 cell count of <200 cells/µL had virtually no detectable cryoglobulins. We fully agree that the CD4 cell count is only a gross measurement of immune competence and that the functional heterogeneity of CD4+ T cells is important in the regulation of immune responses. In addition to the Th1-Th2 dichotomy, CD4+CD25+ regulatory T cells might play an important role in the control of effector cells, particularly in the case of HIV infection, in which they have been shown to repress T cells specific for HIV antigens [3], and one could imagine a similar negative regulation of other pathogen-specific T cells. In addition, regulatory T cells, in a variety of models, have been shown to suppress autoimmunity [4, 5], and they possibly could also contribute to the regulation of mechanisms that lead to cryoglobulin production.

However, use of the threshold CD4 cell count of 200 cells/µL has a clinical value, since numerous studies have documented the safety of an interruption of primary and secondary prophylaxes for opportunistic infections in HIV-infected patients who reach this CD4 cell count while receiving HAART [6], whereas laboratory studies have shown the recovery of pathogen-specific [6] and even HIV-specific [7] T cell responses in patients receiving HAART. Thus, from a clinical viewpoint, the CD4 cell count increase observed in patients receiving HAART reflects a true restoration of immune effectors, although this response is not always normal, as shown in reports describing the so-called immune restoration syndrome, which sometimes leads to an inflammatory condition (sarcodeiosis) or an autoimmune disorder (Graves disease) [8, 9].

We still think that a variety of arguments, mentioned in our article [2], support a role for cell-mediated immunity in the production of HCV-associated cryoglobulins (e.g., the influence of major histocompatibility complex polymorphism), as has been shown for other antibody responses against infectious agents or autoantigens. The inclusion of CD4 cell count in the clinical picture is therefore consistent with these arguments. The situation might be different for HIV-associated cryoglobulins (as described in HIV-positive, HCV-negative patients), for which the quantity of viral antigen (i.e., a high plasma HIV RNA load) seems to be the driving force [10], and, in that situation, the CD4 cell count is, of course, fre-